

~~28. A method executed by a computer under the control of a program, said computer including a memory for storing said program, said method comprising the steps of:~~

- ~~(A) receiving a protein backbone structure with variable residue positions;~~
- ~~(B) establishing a group of potential amino acids for each of said variable residue positions; and~~
- ~~(C) analyzing the interaction of all or part of each of said amino acids with all or part of the remainder of said protein backbone structure to generate a set of optimized protein sequences, wherein said analyzing step includes a Dead-End Elimination (DEE) computation.~~

29. A method executed by a computer under the control of a program, said computer including a memory for storing said program, said method comprising the steps of:

- (A) receiving a protein backbone structure with variable residue positions;
- (B) classifying each variable residue position as either a core, surface or boundary residue;
- (C) establishing a group of potential amino acids for each of said variable residue positions, wherein the group of potential amino acids for at least one of said variable residue position has an amino acid selected from each of at least two different amino acids; and
- (D) analyzing the interaction of all or part of each of said amino acids with all or part of the remainder of said protein to generate a set of optimized protein sequences.

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30. A method according to claim 29 wherein said analyzing step comprises a DEE computation.

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31. A method according to claim 28 or 29 wherein said set of optimized protein sequences comprises the globally optimal protein sequence.

32. A method according to claim 28 or 30 wherein said DEE computation is selected from the group consisting of original DEE and Goldstein DEE.

33. A method according to claim 28 or 29 wherein said analyzing step includes the use of at least one scoring function.

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34. A method according to claim 33 wherein said scoring function is selected from the group consisting of a Van der Waals potential scoring function, a hydrogen bond potential scoring function, an atomic solvation scoring function, an electrostatic scoring function and a secondary structure propensity scoring function.

35. A method according to claim 33 wherein said analyzing step includes the use of at least two scoring functions.

36. A method according to claim 33 wherein said analyzing step includes the use of at least three scoring functions.

A2  
contd

37. A method according to claim 33 wherein said analyzing step includes the use of at least four scoring functions.

38. A method according to claim 33 wherein said atomic solvation scoring function includes a scaling factor that compensates for over-counting.

39. A method according to claim 28 or 29 further comprising experimentally testing at least one member of said set.

40. A method according to claim 31 further comprising the step of:  
generating a rank ordered list of additional optimal sequences from said globally optimal protein sequence.

41. A method according to claim 40 wherein said generating includes the use of a Monte Carlo search.

42. A method according to claim 29 wherein said analyzing step comprises a Monte Carlo computation.

43. A method according to claim 40 further comprising the step of:  
testing some or all of said protein sequences from said ordered list to produce potential energy test results.

44. A method according to claim 43 further comprising the step of:

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SUB  
B4

A2  
contd

analyzing the correspondence between said potential energy test results and theoretical potential energy data.

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45. A recombinant protein comprising an optimized protein sequence generated by the method of claim 28 or 29.

46. A nucleic acid sequence encoding a recombinant protein according to claim 45.

47. An expression vector comprising the nucleic acid sequence of claim 46.

48. A host cell comprising the nucleic acid sequence of claim 46.

49. A method executed by a computer under the control of a program, said computer including a memory for storing said program, said method comprising the steps of:

(A) receiving a protein backbone structure with variable residue positions;

(B) establishing a group of potential amino acids for each of said variable residue positions, wherein the group of potential amino acids for at least one of said variable residue position has a amino acid selected from each of at least two different amino acids; and

(C) analyzing the interaction of all or part of each of said amino acids with all or part of the remainder of said protein backbone structure to generate a set of optimized protein sequences, wherein said analyzing step includes:

i. a Dead-End Elimination (DEE) computation; and,

ii. at least one scoring function selected from the group consisting of a Van der Waals potential scoring function, a hydrogen bond potential scoring function, an atomic solvation scoring function, an electrostatic scoring function and a secondary structure propensity scoring function.

50. A method executed by a computer under the control of a program, said computer including a memory for storing said program, said method comprising the steps of:

- (A) receiving a protein backbone structure with variable residue positions;
- (B) classifying each variable residue position as either a core, surface or boundary residue;
- (C) establishing a group of potential amino acids for each of said variable residue positions, wherein the group of potential amino acids for at least one of said variable residue position has a amino acid selected from each of at least two different amino acids; and
- (D) analyzing the interaction of all or part of each of said amino acids with all or part of the remainder of said protein to generate a set of optimized protein sequences wherein said analyzing step includes:
  - i. a Dead-End Elimination (DEE) computation; and,
  - ii. at least one scoring function selected from the group consisting of a Van der Waals potential scoring function, a hydrogen bond potential scoring function, an atomic solvation scoring function, an electrostatic scoring function and a secondary structure propensity scoring function.--

A2  
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